CHEST™

Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

CHEST Guideline and Expert Panel Report

Darren B. Taichman, MD, PhD, FCCP; Joe Ornelas, MS; Lorinda Chung, MD; James R. Klinger, MD, FCCP; Sandra Lewis, PhD; Jess Mandel, MD; Harold I. Palevsky, MD, FCCP; Stuart Rich, MD, FCCP; Namita Sood, MD, FCCP; Erika B. Rosenzweig, MD; Terence K. Trow, MD, FCCP; Rex Yung, MD, FCCP; C. Gregory Elliott, MD, FCCP; and David B. Badesch, MD, FCCP

OBJECTIVE: Choices of pharmacologic therapies for pulmonary arterial hypertension (PAH) are ideally guided by high-level evidence. The objective of this guideline is to provide clinicians advice regarding pharmacologic therapy for adult patients with PAH as informed by available evidence.

METHODS: This guideline was based on systematic reviews of English language evidence published between 1990 and November 2013, identified using the MEDLINE and Cochrane Library databases. The strength of available evidence was graded using the Grades of Recommendations, Assessment, Development, and Evaluation methodology. Guideline recommendations, or consensus statements when available evidence was insufficient to support recommendations, were developed using a modified Delphi technique to achieve consensus.

RESULTS: Available evidence is limited in its ability to support high-level recommendations. Therefore, we drafted consensus statements to address many clinical questions regarding pharmacotherapy for patients with PAH. A total of 79 recommendations or consensus statements were adopted and graded.

CONCLUSIONS: Clinical decisions regarding pharmacotherapy for PAH should be guided by high-level recommendations when sufficient evidence is available. Absent higher level evidence, consensus statements based upon available information must be used. Further studies are needed to address the gaps in available knowledge regarding optimal pharmacotherapy for PAH.

CHEST 2014; 146(2):449-475

ABBREVIATIONS: 6MWD = 6-min walk distance; AHRQ = Agency for Healthcare Research and Quality; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study; BNP = brain natriuretic peptide; CB = consensus-based; CCB = calcium channel blocker; CO = cardiac output; COI = conflict of interest; CTEPH = chronic thromboembolic pulmonary hypertension; EPC = Evidence-Based Practice Center; ETRA = endothelin receptor antagonist; FC = functional class; FDA = US Food and Drug Administration; GOC = Guidelines Oversight Committee; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; HR = hazard ratio; IOM = Institute of Medicine; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase-5; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; WHO = World Health Organization

Manuscript received April 1, 2014; revision accepted May 5, 2014; originally published Online First June 17, 2014.

AFFILIATIONS: From the University of Pennsylvania (Drs Taichman and Palevsky), Philadelphia, PA; CHEST (Mr Ornelas and Dr Lewis), Glenview, IL; Stanford University and Palo Alto VA Health Care System (Dr Chung), Palo Alto, CA; Brown University (Dr Klinger), Providence, RI; the University of California (Dr Mandel), San Diego, CA; the University of Chicago (Dr Rich), Chicago, IL; Ohio State University (Dr Sood), Columbus, OH; Columbia University Medical Center (Dr Rosenzweig), New York, NY; Yale University (Dr Trow), New Haven, CT; Johns Hopkins University

Summary of Recommendations

Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

1. We suggest that the severity of a pulmonary arterial hypertension (PAH) patient's disease be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, echocardiographic, laboratory and hemodynamic variables in order to inform therapeutic decisions (Grade CB).

2. We suggest that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy (Grade CB).

3. We suggest collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care (Grade CB).

Remark: Appropriate care may require the coordinated efforts of cardiologists, pulmonologists, rheumatologists, primary care, or other specialties.

Treatment Naive PAH Patients Without Symptoms (WHO FC I) and Patients at Increased Risk for the Development of PAH

4. For treatment naive PAH patients with WHO FC I symptoms, we suggest continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy (Grade CB).

5. We suggest that patients at risk for the development of PAH (eg, patients with systemic sclerosis or the presence of a known mutation placing the patient at risk for PAH) be monitored for the development of symptoms of PAH (Grade CB).

6. We suggest also that contributing causes of PH (eg, sleep apnea and systemic hypertension) in patients with PAH be treated aggressively (Grade CB).

Symptomatic Patients With PAH

Vasoreactivity Testing and Use of Calcium Channel Blockers

7. We suggest that patients with PAH, in the absence of contraindications, should undergo acute

FOR EDITORIAL COMMENT SEE PAGE 239
SEE RELATED ARTICLE PAGE 476

vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing (Grade CB).

Remark: Contraindications to acute vasoreactivity testing include a low systemic blood pressure, low cardiac output or the presence of FC IV symptoms. Acute vasoreactivity testing may be complicated by hypotension, and the misinterpretation of results may result in the inappropriate exposure of patients to the risks of a treatment trial with calcium channel blockers (CCBs) without the possibility of clinical benefit. Vasoreactivity testing should be performed by individuals with appropriate training in test performance and interpretation.

8. We suggest that patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB blocker (Grade CB).

9. We suggest that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (Grade CB).

PAH-Specific Pharmacotherapies

Patients With WHO FC II Symptoms:

For treatment naive PAH patients with WHO FC II symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

(Dr Yung), Baltimore, MD; the Intermountain Medical Center and the University of Utah (Dr Elliott), Murray, UT; and the University of Colorado (Dr Badesch), Denver, CO.

Drs Elliott and Badesch contributed equally to this manuscript.

FUNDING/SUPPORT: This study was funded in total by internal funds from the American College of Chest Physicians.

CORRESPONDENCE TO: Joe Ornelas, MS, CHEST, 2595 Patriot Blvd, Glenview, IL 60026; e-mail: jornelas@chestnet.org

DOI: 10.1378/chest.14-0793